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EXTRAHEPATIC COMPARED WITH HEPATIC METABOLISM OF NICOTINE IN THE RAT

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Pulmonary and hepatic metabolism of ^{14}C-labelled nicotine and cotinine was studied in isolated perfused lung and liver of phenobarbital (PB)-pretreated and uninduced rats. The kinetic parameters of nicotine were also investigated in conscious rats receiving nicotine (0.3 mg/kg) either intravenously or orally in order to quantify hepatic first-pass extraction of nicotine in vivo.

The kinetic parameters of the elimination of nicotine from the perfusion circuit demonstrated a relatively high elimination rate in rat lung approaching the capacity of liver when both organs were not induced. The concentration-time profiles of the metabolite cotinine in the perfusate were almost identical in perfused lung and liver. In the untreated conscious rat 89 % of the oral dose reached the circulation as unchanged nicotine indicating a low hepatic extraction ratio of about 10 %. - The turnover of the metabolite cotinine was studied in isolated perfused organs using cotinine as the substrate. In the uninduced liver the elimination half-life was 180 $\pm$ 27 min and the clearance was 0.5 ml/min corresponding to a low value of 4 % for the first-pass extraction. The isolated rat lung exhibits much less activity to metabolize cotinine. Thus a secondary metabolic pathway of cotinine predominantly occurs within the liver.

Phenobarbital treatment had different effects on nicotine metabolism in lung and liver. The clearance of nicotine was induced 2-fold in lung. The pattern of nicotine metabolites in the perfusate, however, was not affected by PB-induction. The pulmonary capacity to metabolize cotinine was not different from uninduced controls. Hepatic nicotine elimination was induced 8-fold by PB, as shown previously for the isolated rat liver. A marked increase of the hepatic first-pass extraction of nicotine was now confirmed for the in vivo situation in which the oral availability of unchanged nicotine dropped to 1.4 %. Yet, despite of the marked induction of the hepatic clearance, the total clearance of i.v. nicotine was only increased 2-fold in the conscious rat. This indicates that an important part of the systemic clearance of nicotine is mediated by extrahepatic organs.

In the perfused liver the elimination parameters of cotinine used as the substrate were increased approximately 10-fold after PB. This is in accordance with the very small amount of cotinine appearing in the plasma after i.v. administration of nicotine to the conscious rat. The pattern of urinary metabolites of nicotine strongly correlated with the induction state. It is concluded that the metabolism of cotinine, which predominantly occurs in the liver, may be a suitable indicator of the PB-inducible cytochrome P-450 isoenzyme(s).